The immunology, serology, and epidemiology of syphilis in the AIDS era

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I will attempt to explain why the stages in the development of immunologic control in syphilis are remarkably similar to the immunology associated with HIV infection and disease progression, and examine serology and epidemiologic evidence which compels us to look at this.

Immunology

There are several animal models for syphilis but there is none for HIV infection. In animal models of human haematopoetic disease such as the simian and feline viruses, a true and active T-cell tropism exists and treatments and vaccines generally have a better effect than in human retroviral disease, precisely because no mechanism for HIV induced T-cell depletion has emerged in seven years of research. *T-pallidum* upon one infection severely depletes T-cells by both direct attack and chemotactic mechanisms. In infected rabbits and congenital human neonates, thymus-dependent areas of the spleen are atrophied. In acquired syphilis (the first infection), cellular immunity and specifically T-helper cells have a very hard time getting the upper hand. A kind of split response seems to occur in syphilis where humoural antibody appears early while the critically needed cellular immunity fails for months or even years, as demonstrated by a failure of T-lymphocytes to transform normally in the presence of specific treponemal antigen and by skin tests of the delayed hypersensitivity type remaining negative.

On its own, humoural antibody cannot seemingly control syphilis, but once the lymphocyte transformation is successful the disease becomes uninfectious and latent. The literature is controversial concerning the degree of *non-treponemal-specific* immune suppression during the development of this relative immunity. Some authors have demonstrated defects in response to various mitogens. The route of treponemal inoculation seems critical, with the IV method resulting in the greatest immune suppression in the rabbits' CMI. Acquiring treponemal disease in the anus or colon is probably getting closer to the IV method of inoculation, with the primary insult simply being more direct. Chancres probably cause gradual sensitization of most healthy hosts since they are a host-controlling phenomenon.

Of course, this is not AIDS, and treatment with penicillin early in the infection promptly restores normal responses to other antigens by removing most of the *t-pallida*. In humans—the only natural host—when treatment is either withheld or neglected, the situation is more complex. When effective immunity is incubating in a human host, a non-specific humoural hypergammaglobulinaemia often exists. In untreated syphilis of greater than, say, six months duration, treatment often fails to reverse this hyperimmune state. Many investigators in the seventies felt that auto-immunization had begun. Treponemes coated with host immunoglobulins and resultant circulating immune complexes, along with persistence in privileged sites, were the main parasitic strategies cited. Persistence is also suspected because, once activated, syphilitic lymphocyte sensitivity is not reversed by therapy. Classical syphilology also warns us that any form of treatment during the incubation of this critically necessary CMI basically destroys it. The signs and serology of a superinfection will not appear normally during the incubation of the immunity and may not appear at all later in the process. Infectious syphilis correlates with the absence of the effective cellular immunity.

Associated with HIV infection there is also the non-specific humoural gammopathy and a defect in CMI, so immunologically both the cellular and humoural responses in syphilis may be AIDS inducing. The excessively long period needed to develop effective CMI to *t-pallidum* is a unique phenomenon in infectious disease and is the subject of much study. In essence the failed incubation of immunity to syphilis could be the best model for induction of AIDS-like immunology.

Syphilis has an altered profile in re-infected, superinfected, or immunologically weakened persons. The

syphilis screen test (VDRL) detects some of many auto-antibodies. It is basically 80 years old except for substitution of lecithin and cardiolipin in the place of beef heart antigen, and sensitivity and specificity were sacrificed for the sake of reproducibility in immunologically normal or average persons. I can provide many references to support my concerns that this test failed to protect the gay community and other sexually active persons from syphilis in the sixties and seventies. Many authors felt that intact CMI was critical for normal VDRL reaction or at least that it was somehow a critical component.

Epidemiology

The epidemiology of syphilis in the AIDS era gives considerable weight to the above assertions. The CDC published its fact sheet in 1980 acknowledging 325,000 untreated cases of syphilis in the United States and an annual new infection rate of 40 to 50 thousand cases. The British suggest that syphilis was under reported, under diagnosed, and under treated in the United States for 20 years. There are several excellent references. In the seventh edition of Harrison, it is stated that only 12% to 19% of middle class white syphilis was reported to public health authorities. I cannot imagine the treating physicians doing the contact tracing for free. By the late seventies, approximately 60% of this syphilis was occurring in multipartner gay males, yet in 1990, I have not seen one AIDS death attributed to opportunistic syphilis. Many opportunistic infections in AIDS are diseases which seem to require adequate CMI for protection, such as the mycobacteriosis. TB and syphilis always used to be together, with syphilis generally making TB worse, but now it is HIV that has taken the place of "the great masquerader" as exacerbater of this once ubiquitous mycobacterium. A well-known syphilologist in the thirties found 80% of his syphilis hospital admissions had lost their ability to react in the BCG skin reaction, while 80% of non-syphilis admissions reacted normally. TB was 80% prevalent in many urban American centres in the pre-antibiotic era. If HIV antibody is not a marker for untreated and deadly syphilis, then where are the expected serologic and clinical sequellae of a quarter million cases of untreated gay male syphilis? I would like to suggest that many of these cases accelerated the AIDS in our friends.

Serology

The postulated failure of incubating CMI to syphilis would explain the selective and intermittent treponemal antibody loss we seem to find in non-end stage HIV associated B-cell polyclonal hypergammopathy because humoural immunity may not be turned on. Furthermore, even if turned on (a reactive treponemal test), many of the B-cells may not convert to antibody-secreting cells due to various postulated factors, resulting in further immune suppression as unhindered treponemes have a freer reign, probably dividing very slowly. For a first time treponemal infection, the specific serology probably means control, but in reinfected persons (many gay males) we need to look at IgM with a capture assay, and do immunoblots, comparing them with controls (HIV negative non-AIDS associated syphilis). A reactive IgM capture assay (Mercia) could prove active syphilis in some persons with negative treponemal tests because of the greater sensitivity of this test, due to a monoclonal antigen reagent and lack of absorption and dilution. In less well people the presently accepted treponemal tests lack sensitivity. Of course, a reactive IgM test may be a good prognostic marker, indicating possible benefit from therapy. Undoubtedly, specific treponemal peptides function as super-antigens, and defective humoural antibody lets these toxic substances loose even though the humoural tests react the same. Lyme disease progression is an excellent precedent for sero-negative or sero-defective spirochetal disease. Half of Lyme reactors also react to the FTA-Abs.

One venerable syphilologist, Dr. Paul Hardy at Johns Hopkins, told me in no uncertain terms that persons whose blood immobilizes treponemes in the TPI still harbour the infectious agent, yet we offer no prophylaxis to the thousands of HIV infected persons with reactive TPI serology basing this decision on the one-time infected and treated model. James N. Miller chooses to interpret reactive FTA-Abs as false positives in high-risk persons when the TPI is negative, citing the TPI's enviable specificity and polyclonal activation. I suggest the patients are too defective to immobilize the organism in the living complement fixation test, but react by binding certain antibodies to the fixed slide FTA-Abs. Syphilis serology generally cannot show super-infection in latents except by anamnestic rises of treponemal antibody. These tests were never offered in the sixties and seventies.

PCR (polymerase chain reaction) work in syphilis has enviable specificity and sensitivity, we would assume, but it is confusing because when attempted in an STD clinic in England most risk-group patients reacted, HIV notwithstanding. It is very difficult to decide which part of the sequence of the treponeme to amplify, and of course this test would be useless in any area where yaws was endemic because most children born to mothers treated in the yaws campaign themselves have high titre TPI serology for life. The Dutch have work in print which may help in the PCR area.

[I then discussed several interesting experiences in the presumptive treatment of syphilis in CDC IV persons and several cases of intriguing serology.]

The ususal but not universal failure of standard syphilotherapy to reverse or alter AIDS is no argument for the exclusion of persistent treponemal disease as an AIDS exacerbater in the absence of competent CMI. Host antibody, especially the anti-connective tissue antibodies (VDRL), is associated with transverse fission and beta-lactam drug efficacy. An epidemic of syphilis in its later forms was predicted by investigators 20 years ago. We in the AIDS field have generally failed to examine treponemal infection due to the prevailing HIV theory.

Summary

In summary, syphilis is an immune-complexing disease, an auto-immune disease, a T-cell depleting disease, and an initiator of non-specific humoural immunity. There is also an animal model. HIV meets less of these disease-inducing criteria except by the antibody association and other imperfect markers. Syphilis is tough to treat once the auto-immunization has begun and biological cure may be impossible. The immunologic profile does not reverse in many treated humans. A further syphilitic infection on top of this state would behave unpredictably since the classical picture of a refractory state has undoubtedly been fractured by modern antibiotics. Syphilis appears to be totally absent from actual AIDS, as opposed to early HIV infection when it appears *only* in its classical presentation, this despite overwhelming epidemiologic and immunologic evidence to the contrary. Antibody was always the pillar of syphilis diagnosis but now no more. Treponemal antigen was always hard to demonstrate even in overt examthem high titre VDRL syphilis, but especially in later syphilis. Rabbit inoculation is very under sensitive in later syphilis. We need to apply some of the technology learned in the HIV era to the syphilis question.

We must investigate auto-immunity in syphilis and look behind the simple anti-cardiolipin reaction. The smallest amount of treponemal antigen could cause the AIDS-like immunology in susceptible persons.

Some HIV questions which force us to look at other infections with tropisms for T-cells:

Why do Ugandans have one tenth the AIDS rate of gay Americans for the same number of HIV positives despite a total lack of accelerated HIV care in central Africa? Uganda has a WHO supervised case definition and reporting system, and a recent article in the NEJM confirms that AIDS is not under reported in this country. I suggest this is because they are mostly monogamous heterosexual couples without continued new sexual infections, such as *t-pallidum*, and their HIV infection is probably congenital and not dangerous.

Why do some HIV experts (Salk Institute) assert HIV is several centuries old and has been causing AIDS in Africa (slim disease) for centuries? African doctors have told me in no uncertain terms that AIDS is new, *period*, and that slim disease is not HIV disease. Who do we believe? I vote for the clinician. Previously healthy persons get sick and die just like in America, with sexual activity and STD being their behaviour in common with the AIDS scene in America. Again syphilis is mysteriously rare in African CDC III and IV despite the disastrous syphilis serology in sub-Saharan Africans reported repeatedly in the European STD literature.

Why did we not see AIDS migrating with the slave trade for two centuries before the Civil War?

Could not yaws eradication and effective antimalarials have altered the natural immunity to treponemal disease in Africa, along with all of the above mechanisms postulated for American syphilis?

Is it reasonable that two mutations, HIV-I and HIV-2, could have happened to cause AIDS at almost the same time and then attain remarkable world-wide dissemination all in less than a generation, despite its lack of infectiousness without STD ulceration? Isn't it time we asked the question whether multiple STDs acting synergistically activate HIV infection? We could then end up with many HIV positives without the fatal co-factors, such as syphilis and TB, who live for decades. Some expert retrovirologists find little evidence for biological activity for retroviruses like HIV.

Is it unreasonable to assume that AZT benefit may be due to non-viral drug efficacy or transfusions?

Why doesn't 10 to 200 times infectious dose with HIV cause sustained infection in any animal model?

Why do all HIV markers wind up being less than reliable predictors of disease progression? Inverted cell ratios and low T4s do not reliably predict HIV antibody status in Trinidad. 65% of these men *reported* a history of syphilis and mean age was 22 years.

What could be other explanations for the Pasteur Institute's recent in vitro observations that antimicrobials in long term therapy may help AIDS? Dr. Steve Caiazza probably tried his uncontrolled experiment too soon in the crisis.

Why is the mean time free of AIDS growing to over 30 years in several risk groups?

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